Role of the tumor suppressor gene, p16INK4a, in regulating stem cell phenotypes in embryonic stem cells and human epithelial cells.

Grant Award Details

Role of the tumor suppressor gene, p16INK4a, in regulating stem cell phenotypes in embryonic stem cells and human epithelial cells.

Grant Type: SEED Grant

Grant Number: RS1-00444

Investigator:

Name:	Thea Tlsty
Institution:	University of California, San Francisco
Type:	PI

Disease Focus: Cancer

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $614,784

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: NCE

View Report

Grant Application Details

Application Title: Role of the tumor suppressor gene, p16INK4a, in regulating stem cell phenotypes in embryonic stem cells and human epithelial cells.

Public Abstract:

The roles of stem cells are to generate the organs of the body during development and to stand ready to repair those organs through repopulation after injury. In some cases these properties are not correctly regulated and cells with stem cell properties expand in number. Recent work is demonstrating that the genes that control stem cell properties are sometimes the same genes that are mutated in cancer. This means that a cell can simultaneously acquire stem cell properties and cancer properties. In order to effectively use stem cells for therapeutic purposes we need to understand the link between these two programs and devise ways to access one program without turning on the other. In other words, we would like to expand stem cell populations without them turning into cancer.

Recent work in our laboratory has found that the reduction of a specific tumor suppressor gene, p16, not only removes an important barrier to cancer but also confers stem cell properties within the cell. Cells that have reduced p16 activity can turn on a program that increases and reduces expression of specific genes that control differentiation. In this proposal we will test whether the continued reduction of this tumor suppressor gene creates human embryonic stem cells (hESC) that are unable to differentiate. We hypothesize that the lack of p16 represses multi-lineage potential by activating an epigenetic program and silencing genes that drive differentiation. To test this hypothesis we will first determine if lack of p16 activity is necessary for hESCs to develop into different cell types. Second, we will determine if continued lack of p16 activity is sufficient to inhibit differentiation of hESCs. Finally, we will determine if transient lack of p16 activity is sufficient for a non-stem cell to exhibit properties of a stem cell after propagation in a stem cell niche.

Since these types of events are potentially reversible, targeting such events may become clinically useful. These new observations identify novel opportunities. They provide potential markers for determining if someone is susceptible to cancer, as well as, providing potential targets for prevention and therapy. We hypothesize that these properties are critically relevant to the formation of cancer and will provide insights into the role of epigenetic modifications in disease processes and stem cell characteristics.

Statement of Benefit to California:

Stem cells hold great potential to help us in repairing injured body parts or replacing damaged organs. In order to realize this potential the rules that control stem cell behavior need to be understood. Recent work is demonstrating that the genes that control stem cell properties are sometimes the same genes that are mutated in cancer. In the proposed study we hypothesize that we may learn about a fundamental switch that not only controls stem cells but also controls the formation of a cancer cell. In understanding how this switch works we may be able to identify biomarkers that indicate when a normal looking cell will become a cancer cell or identify a drug that will allow us to stop the potential cancer cell from increasing in number. Since cancer is a common disease in California, any insights we can gain to battle this disease will benefit the citizens of our State.

There is also another side to the insights that may arise from the work in this proposal. Currently we believe the roles of stem cells are to generate the organs of the body during development and to stand ready to repair those organs through repopulation after injury. We do not know how to encourage a stem cell to repair, for example, some heart tissue rather than some bone tissue. If we could understand the code that directs the stem cells to differentiate in the proper fashion into one tissue or another, we could use these cells for clinical benefit. The pathways we are studying in this proposal tell the stem cells which genes to silence and which to activate. This is the program that allows the one original cells of your body (the embryo) to diversify into the multitude of specialized cells that work together to make a functioning person (eye cells, skin cells, nerve cells, etc.). In order to effectively use stem cells for therapeutic purposes we need to understand how they code their decisions and whether they can be changed after they have been set. These insights would allow us to aid in maintaining the health of the citizens of California.

Finally, if we do gain insight into the code that regulates the differences between cancer cells and stem cells, this information would be the basis of a new area of biotechnology. The generation of knowledge in this area would help in the development of companies, the recruitment of bright young minds and in the fiscal health of our State

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